ORNITHINE AND HOMOCITRULLINE PROVOKES IMPAIRMENT OF REDOX HOMEOSTASIS IN CORTICAL ASTROCYTES

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Introduction: Hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome is an inborn error of metabolism caused by a defect in the transport of ornithine (Orn) into mitochondrial matrix leading to accumulation of Orn, homocitrulline (Hcit) and ammonia. Affected patients present a variable clinical symptomatology, including developmental delay, progressive encephalopathy with mental regression, motor dysfunction, hypotonia and coagulation abnormalities. Although neurological manifestations are common, the pathogenesis of brain injury in this disease is poorly known. Objectives: Since astrocytes are important for neuronal protection and are susceptible to damage by neurotoxins, we investigated the effects of Orn and Hcit, on redox homeostasis, cytokine production and mitochondrial function in cortical cultured astrocytes. Material and methods: Cerebral cortex from neonatal cortex was dissected and from it we cultured astrocytes. Reduced glutathione, 2′-7′-dichlorofluorescein diacetate (DCF-DA) oxidation), TNF-α, IL-1, IL-6, NF-κβ and MTT reduction were measured in the presence of Orn or Hcit. Discussion and results: Hcit decreased MTT (mitochondrial function), reduced glutathione and increased reactive species formation (DCF-DA oxidation). In contrast, Orn only decreased MTT. Cytokine production (TNF-α, IL-1 and IL-6) and NF-κβ were not altered by these metabolites. Conclusions: Taken together, the present data show that Orn and Hcit disrupt astrocytic redox homeostasis, a pathomechanism that may contribute to the neuropathology of patients affected by HHH syndrome.

Key words: HHH syndrome, redox homeostasis, astrocytes

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